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Motor Function Under Lower and Higher Controlled Processing Demands in Early and Continuously Treated Phenylketonuria

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This study examined motor control in 61 early and continuously treated patients with phenylketonuria (PKU) and 69 control participants, aged 7 to 14 years. The pursuit task demanded concurrent planning and execution of unpredictable movements, whereas the tracking task required a highly automated circular movement that could be planned in advance. PKU patients showed significantly poorer motor control in both tasks compared with control participants. Deficits were particularly observed for younger patients (age < 11 years). Differences between control participants and PKU patients were significantly greater in the pursuit task compared with the tracking task, indicating more serious deficits when a higher level of controlled processing is required. Correlations with historical phenylalanine levels indicated a later maturation of the level of control required by the pursuit task compared with the tracking task.

Phenylketonuria (PKU) is an autosomal recessively inherited metabolic disease in which the essential amino acid phenylalanine (Phe) cannot be converted into tyrosine (Tyr). Untreated, PKU results in largely increased Phe con-

centrations in blood and tissues and low to normal Tyr concentrations, leading to severe mental and neurological retardation (Scriver, Kaufman, Eisensmith, & Woo, 1995). Treatment is based on a Phe-restricted diet. The diet consists of severe restriction of natural protein supplemented with all amino acids but Phe to compensate for a shortage of amino acids through regular protein intake.

In early treated PKU, predominantly subclinical neurological impairments have been observed, among which are deficient proprioception, subclinical deficits in central motor and sensory pathways, and minor sensory neuropathy (Ludolph, Ullrich, Nedjat, Masur, & Bick, 1992). In addition, increased tremor and decreased hand–wrist steadiness, finger–hand dexterity, and hand–wrist speed have been observed (Pietz et al., 1998).

Reduced fine motor abilities and visuomotor integration have been regularly reported in early treated PKU patients (Arnold et al., 1998; Pietz et al., 1998; Seashore, Friedman, Novelty, & Bapat, 1985; Weglage, Pietsch, Fünders, Koch, & Ullrich, 1995). The fact that higher integrative functioning was usually required to perform these tasks is in agreement with the type of neuropsychological deficits most frequently found in treated PKU: executive function deficits, which have often been associated with concurrent or historical blood Phe levels (Diamond, 1994; Diamond, Prevor, Callender, & Druin, 1997; Huijbregts, De Sonnevile, Licht, Sergeant, & Van Spronsen, 2002; Huijbregts, De Sonnevile, Licht, Van Spronsen, et al., 2002; Ris, Williams, Hunt, Berry, & Leslie, 1994; Smith, Klim, Mallozzi, & Hanley, 1996; Weglage, Pietsch, Fünders, Koch, & Ull-

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rich, 1996; Welsh, Pennington, Ozonoff, Rouse, & McCabe, 1990). In addition to these findings, impaired visuomotor reaction time (RT; Burgard, Rey, Rupp, Abadie, & Rey, 1997), vigilance and sustained attention (Burgard et al., 1997; De Sonnevile, Schmidt, Michel, & Batzler, 1990; Huijbregts, De Sonnevile, Licht, Van Spronsen, et al., 2002; Schmidt, Burgard, & Rupp, 1996), and interhemispheric transfer (Banich, Passarotti, White, Nortz, & Steiner, 2000; Gourovitch, Craft, Dowton, Ambrose, & Sparta, 1994) have been demonstrated.

Pathophysiological Mechanisms

Currently, no single pathophysiological mechanism can explain the cognitive and neurological impairments of PKU. Damaged myelin, the occurrence of which has frequently been reported in PKU (e.g., Bick et al., 1991; Cleary et al., 1994; Pietz et al., 1996; Thompson et al., 1993), interferes with speed of information processing (Koester, 1991; Rowland, 1991). On the other hand, increased blood Phe levels disrupt normal large neutral amino acid (LNAA) transport ratios across the blood-brain barrier, resulting in decreased availability of LNAAs including Tyr in the brain (Medical Research Council [MRC] Working Party on Phenylketonuria, 1993; Pietz et al., 1999). The prefrontal cortex (PFC) dysfunction hypothesis for PKU (Diamond et al., 1997; Welsh et al., 1990) is based on the specific sensitivity of prefrontal dopaminergic neurons to even small reductions in Tyr (Tam & Roth, 1997). These neurons lack the synthesis-modulating autoreceptors present in other brain areas and consequently have a faster breakdown rate than other dopaminergic neurons (Bannon, Bunney, & Roth, 1981; Chiodo, Bannon, Grace, Roth, & Bunney, 1984).

Cognitive functions that are particularly sensitive to catecholaminergic (dopaminergic and noradrenergic) modulation through the dorsolateral PFC (DLPFC) are those involved in on-line manipulation and monitoring of cognitive representations within working memory (WM; Arnsten, 1998; Luciana & Collins, 1997; McDowell, Whyte, & D'Esposito, 1998; Mehta et al., 2000; Robbins, 2000). Within the two-level model of executive control, DLPFC is activated when conscious active control of planned behavior and cognition is required (Owen et al., 1999; Petrides, 1994, 2000). The two-level model further incorporates a maintenance component, which is involved in holding information in short-term memory and mnemonic operations such as active selection, comparison, and judgment of stimuli held in short-term and long-term memory (Petrides, 2000).

Tasks showing deficient performance in treated PKU usually required continuous monitoring of cognitive representations within WM for a variety of reasons, such as inhibition of prepotent responding (Diamond et al., 1997; Huijbregts, De Sonnevile, Licht, Van Spronsen, et al., 2002; Weglage et al., 1996; Welsh et al., 1990) and switching between attentional sets (Huijbregts, De Sonnevile, Licht, Sergeant, & Van Spronsen, 2002; Weglage et al., 1996). Moreover, in PKU a relationship has been observed between elevated blood Phe level, reduced dopamine me-

tabolites in cerebrospinal fluid, and impaired performance of a dual-task with high monitoring demands (Krause et al., 1985).

Role of Dorsolateral Prefrontal Cortex in Motor Function

The involvement of (right) DLPFC when continuous monitoring or conscious control of action is required in motor function has been illustrated in a number of studies (e.g., Fink et al., 1999; Rao, Rainer, & Miller, 1997; Seitz, Stephan, & Binkofski, 2000). Fink et al., for example, showed an increase of activation in the right DLPFC only when a mismatch occurred between intention, proprioception, and visual feedback during a task involving either in-phase or out-of-phase bimanual movements, using a mirror to alter visual feedback. By replacing visual feedback from the left hand by the mirror image of the right hand, participants saw in-phase movements despite performing out-of-phase movements. This manipulation resulted in specific activation in the right DLPFC.

Additional evidence for the role of PFC in control of action (movement) stems from human lesion studies (e.g., Heilman, Bowers, Coslett, Whelan, & Watson, 1985; Seitz et al., 2000). Seitz et al. (2000) reported greater activation of the ipsilesional PFC in stroke patients than in healthy individuals while performing unilateral finger-movement sequences and concluded that patients with a specific brain lesion affecting the sensorimotor system engage a comparable control strategy for a simple task such as normal people do under enhanced task difficulty.

In motor function, the match between intended and actual movements is usually achieved automatically (Jeannerod, 1997). Novel tasks, however, or situations that produce conflict or incongruence between intentions and sensorimotor consequences involve awareness of sensory feedback and conscious control of action (Wolpert, Ghahramani, & Jordan, 1995). A number of studies have shown DLPFC involvement during new motor learning (Jenkins, Brooks, Nixon, Frackowiak, & Passingham, 1994; Jueptner & Weiller, 1998; Middleton & Strick, 2000; Pascual-Leone, Wasserman, Grafman, & Hallett, 1996; Sakai et al., 1998). PFC activity decreases after practice (Jueptner et al., 1997).

Fuster (2000) has argued that DLPFC mediates cross-temporal contingencies between perception and movement. This is supported by studies showing activation in various prefrontal regions during cross-temporal integration tasks (Owen, Morris, Sahakian, Polkey, & Robbins, 1996; Swartz et al., 1995) and PFC cell recordings during a double-contingency task (Quintana & Fuster, 1992). Two categories of "memory cells" in the PFC have been identified: those reflecting short-term memory and those involved in the setting of the neuromotor apparatus for response (attentive set neurons). Integration by DLPFC of perception and action is especially required in novel or complex situations. When behavior becomes more automatic (or is not experienced as new or complex) "actions are integrated in lower structures (e.g., premotor cortex, basal ganglia) and the

processing of sensory inputs is shunted at lower levels of the cycle" (Fuster, 2000, p. 335).

When the automatic-controlled distinction is applied to the tasks administered in the present study, the tracking task, which involves drawing a circle (see the Method section) requires less controlled processing than the pursuit task, in which participants must follow a randomly moving target on the computer screen (see the Method section). The pursuit task requires concurrent planning and execution of continuously changing and therefore always "new" movements. In contrast, the tracking task requires the drawing of a well-known, supposedly well-practiced figure that can be planned in advance of its execution. On the basis of the evidence of DLPFC involvement in motor function when continuous monitoring or control of action is required (e.g., Fink et al., 1999; Jenkins et al., 1994; Jueptner et al., 1997; Rao et al., 1997; Seitz et al., 2000) and the close interaction of motor control capacities with executive functioning (e.g., Diamond, 2000), we hypothesized that the requirement of continuous monitoring of task performance extends beyond traditional executive function tasks and that the amount of monitoring required determines the degree of deficits for PKU patients.

Developmental Time Tables of Processing Speed and Aspects of Working Memory

The degree of deficits in PKU has often been associated with concurrent and historical Phe levels (Diamond et al., 1997; Huijbregts, De Sonnevile, Licht, Van Spronsen, et al., 2002; Smith et al., 1996). High Phe levels during critical age periods may interfere with the development of cognitive abilities. Whether high Phe levels have a general deteriorating influence on speed of information processing or affect specific cognitive abilities is subject to ongoing debate.

A number of studies have shown strong associations between the development of processing speed and development of WM capacity and large attenuation of the age-related influences on cognitive measures after statistical control for measures of processing speed (Cerella & Hale, 1994; Fry & Hale, 1996; Kail & Park, 1994; Kail & Salthouse, 1994; Salthouse, 1996). Fry and Hale (2000) conducted an extensive review on developmental relationships between processing speed, WM, and fluid intelligence, and concluded that all follow a similar time course. However, a number of studies have shown that particularly in children not all age-related improvement in WM and/or intelligence could be accounted for by age-related differences in the speed of processing (Fry & Hale, 1996; Kail & Park, 1994; Miller & Vernon, 1996). In addition, note that WM was often measured by span tasks (e.g., Fry & Hale, 1996; Kail & Park, 1994; Miller & Vernon, 1996). In a study using a wide variety of WM tasks, the correlation between WM capacity and processing speed was lower than in studies using span tasks (Kyllonen & Christal, 1990). Age-related changes in WM measured by span tasks may represent development of the maintenance component of WM, whereas age-related changes in WM that are not predicted by age-related changes in processing speed may be changes

in the manipulation or monitoring functions. This would corroborate evidence for different developmental trajectories for different parts of the brain, with respect to both a gradual decrease in synaptic density (pruning) and a gradual increase of cerebral white matter (myelination). Dorsolateral PFC, which is involved in monitoring of WM content, shows the latest maturation (e.g., Bourgeois, Goldman-Rakic, & Rakic, 1994; Casey, Giedd, & Thomas, 2000; Huttenlocher, 1997; Pfefferbaum et al., 1994).

Evidence has also been provided for concomitant maturation of motor function and WM (Diamond, 2000). Development of processing speed, motor function, and WM capacity proceeds gradually, resulting in an increasing capacity to perform complex tasks, approaching an adult level during (early) adolescence (Becker, Isaac, & Hynd, 1987; Cerella & Hale, 1994; Chelune & Thompson, 1987; Welsh, Pennington, & Groisser, 1991). Adult-level performance of less complex tasks is reached earlier in development (Del Giudice et al., 2000; Diamond, 1990; Diamond & Taylor, 1996; Huijbregts, De Sonnevile, Licht, Van Spronsen, et al., 2002; Levin et al., 1991; Luciana & Nelson, 1998; Welsh et al., 1991; Zelazo, Carter, Reznick, & Fry, 1997). Del Giudice et al. (2000), for example, investigated development of visuospatial and grapho-motor capacities during the preschool (3–5 years) and early school years (8–9 years). Ceiling effects were reported for a visual motor task comparable with the tracking task of the present study in the 3.5-to-4-year age group. Executive grapho-motor abilities (copying 10 different models) continued to develop throughout the first school years.

Considering the different characteristics of the tasks used in the present study, we hypothesized that the cognitive capacities or the level of monitoring required by the tracking task will be present earlier in life than for the pursuit task. This hypothesis was tested by studying the relation of Phe levels during the first 10 years of life with task performance. It was predicted that high Phe levels during developmentally critical age periods would adversely affect the level of controlled motor processing during these age periods and in the following years.

Method

Participants

Of the Dutch national population of PKU patients aged between 7 and 14 years (approximately 85 patients), 67 participated in neuropsychological examinations performed at the treatment centers where they received regular follow-up care. All had been treated early (< 1 month after birth) and dietary status was continuously monitored, aiming at Phe levels between 200 and 500 $\mu\text{mol/L}$. Participants were excluded if they (a) had a diagnosis of non-PKU hyperphenylalaninemia (2 patients); (b) followed special education (for learning- or behaviorally impaired children; 2 patients, 1 control participant); (c) had IQ scores under 75 (2 patients, 1 control participant); or (d) showed extreme outlier scores (cases deviating from the mean more than 3 times the interquartile range; 2 control participants). A total of 61 PKU patients were included in the statistical analysis. Of the 73 healthy control participants aged 7 to 14 years, who were recruited from the patients' families or through newspaper advertisements, 69 were

included in the statistical analysis. Mean IQ scores of control participants ($M = 108.2$) differed significantly, $F(1, 128) = 11.6$, $p < .05$, from PKU patients ($M = 97.3$).

A blood sample was taken from the PKU patients before the start of the assessment to determine concurrent Phe level. Historical Phe levels were provided by TNO Prevention and Health in Leiden, the Netherlands, where all Phe levels obtained at regular and irregular medical examinations are collected. The number of Phe measurements was generally very high during the first year(s) of life following the diagnosis of PKU, after which it gradually decreased until a mean of eight measurements in the 10th year of life (see Table 2). When a PKU patient became ill or showed suboptimal dietary control, the number of measurements within relatively short time spans increased, hence the irregular intervals.

Written informed consent was obtained from patients' parents or caretakers before the start of the study. The study was approved by the ethical committees of the treatment centers and by the Dutch National PKU Steering Committee.

On the basis of the most common treatment recommendations (National Institute of Health Consensus Statement Online, 2000), PKU patients were allocated to a PKUlo group when they had concurrent Phe levels $\leq 360 \mu\text{mol/L}$, and to a PKUhi group when they had concurrent Phe levels $> 360 \mu\text{mol/L}$. In addition, participants were allocated to a younger group (age < 11 years) or an older group (age ≥ 11 years). Table 1 provides summary statistics for control participants, PKUlo patients, and PKUhi patients overall and for the younger and older age groups separately.

Tasks and Measures

Three tasks (baseline speed, tracking, and pursuit) of the Amsterdam Neuropsychological Tasks (ANT; De Sonneville, 1999) were administered. Baseline speed measured simple visuomotor RT. In the center of the computer screen, a cross was displayed serving as fixation point, which after a random time interval (500–2,500 ms postresponse) changed into a white square. Upon such a change, participants were required to press the mouse button as fast as possible. A response had to be made between 150 and 5,000 ms, otherwise the trial was replaced. The task consisted of two parts with 32 trials for the preferred hand in Part 1 and 32 trials for the nonpreferred hand in Part 2. Mean RT (calculated over both the preferred and the nonpreferred hand responses) was entered for statistical analysis.

The tracking task required participants to trace the mouse cursor in between an outer (radius 8.5 cm; 3.34 in.) and an inner circle (radius 7.5 cm; 2.95 in.) presented on the computer display. The cursor had to be moved in clockwise direction once with the right hand and once in counter-clockwise direction with the left hand. The ANT program divided the trajectory into 60 radially equal segments and computed the mean distance between the cursor trajectory and the midline per segment, resulting in 60 deviation scores. Mean deviation (accuracy of movement) and standard deviation of the trajectory (stability of movement) that was followed were the dependent measures used for statistical analysis.

The pursuit task required participants to follow a target (an asterisk) that randomly moved across the computer screen with the mouse cursor as closely as possible. The task had to be executed with each hand over a time period of 60 s. The ANT program computed the mean distance between the mouse cursor and the moving target per second, resulting in 60 deviation scores. Mean deviation of the moving target (accuracy of movement) and standard deviation of the trajectory (stability of movement) that was followed were included in statistical analysis.

Data Analysis

Mean RT in the baseline speed task was analyzed in a general factorial analysis with two between-subjects variables: group (controls vs. PKUlo vs. PKUhi) and age (young: age < 11 years vs. old: age ≥ 11 years).

To compare performance on the tracking and the pursuit tasks a multivariate repeated measures analysis was performed with task type as the within-subjects variable (tracking vs. pursuit) and mean deviation and standard deviation as dependents. Group and age were between-subjects variables. Mean RT in the baseline speed task was included as a covariate. Contrast analyses were performed to examine the differences between control participants and PKU patients and between PKUlo and PKUhi patients (1st and 2nd Helmert contrasts, respectively). In order to examine different patterns of results in the two age groups, post hoc comparisons (Tukey's honestly significant difference [HSD]) were performed for younger and older participants separately.

One-tailed partial correlations controlling for age were calculated to examine the relationship between performance on the three tasks (mean RT in the baseline speed task and accuracy and stability in the tracking and pursuit tasks) and a range of variables:

Table 1
Summary Statistics for Control Participants, PKUlo Patients, and PKUhi Patients

Group	N	Age (SD)	C Phe (SD)	Min	Max	IDC (SD)	IQ (SD)
Controls							
Young	37	9.29 (1.25)					108.6 (12.4)
Old	32	12.99 (1.19)					107.2 (12.2)
Total	69	11.01 (2.22)					108.2 (12.1)
PKUlo							
Young	12	9.24 (1.61)	232 (78)	68	350	275 (54)	102.0 (8.3)
Old	12	12.97 (1.24)	203 (118)	30	355	306 (67)	91.6 (7.3)
Total	24	11.10 (2.37)	218 (99)	30	355	292 (62)	95.9 (9.1)
PKUhi							
Young	16	8.96 (0.89)	551 (142)	380	912	389 (164)	101.8 (12.2)
Old	21	12.59 (1.08)	673 (219)	375	1,043	370 (98)	95.9 (12.5)
Total	37	11.02 (2.07)	620 (197)	375	1,043	378 (130)	98.0 (12.4)

Note. Young denotes age < 11 years; old denotes age ≥ 11 years. PKUlo = low phenylketonuria: concurrent phenylalanine (Phe) level $\leq 360 \mu\text{mol/L}$; PKUhi = high phenylketonuria: concurrent Phe level $> 360 \mu\text{mol/L}$; C Phe = concurrent phenylalanine in $\mu\text{mol/L}$; Min = minimum; Max = maximum; IDC = Index of Dietary Control (mean of all half-year median Phe levels until day of testing) in $\mu\text{mol/L}$.

IQ, socioeconomic status (SES), start of treatment (SOT: in days), concurrent Phe level, the Index of Dietary Control (IDC: the mean of all half-year median Phe levels until the day of testing), mean Phe level during the first month of life, and mean Phe levels of the first 10 years of life (i.e., every time the mean of two consecutive half-year median Phe levels). Taking the means of half-year median Phe levels to constitute IDC has been shown to result in high internal validity (strong correlations with other indices) and external validity (strong relation with the revised Wechsler Intelligence Scale for Children [WISC-R IQ]; Rupp & Burgard, 1995).

Results

Baseline Speed

Groups differed significantly with respect to mean RT, $F(2, 124) = 4.0, p < .05$. Contrast analysis (Helmert) showed significantly faster responding by control participants compared with PKU patients (contrast estimate [CE] = $-33.1, p < .05$). No significant difference between PKUlo and PKUhi patients was observed. Younger participants were slower than older participants, $F(1, 124) = 47.9, p < .001$, but no interaction between group and age was observed (see Figure 1).

Tracking and Pursuit

PKU patients performed significantly poorer than control participants on the tracking and pursuit tasks, $F(4, 246) = 7.4, p < .001$. Contrast analyses showed significant differences for both accuracy and stability of performance between control participants and PKU patients (M CE: $-0.446, p < .001$; SD CE: $-0.487, p < .001$). The differences between PKUlo and PKUhi patients did not reach significance. Younger participants showed less accuracy and stability of performance compared with older partici-

pants, $F(2, 122) = 6.3, p < .05$. A significant interaction between group and age, $F(4, 246) = 3.5, p < .05$, indicated that group differences were particularly evident among the younger participants (see Figure 2). Post hoc analyses (Tukey's HSD) confirmed significant differences between younger control participants and both PKU groups. Mean differences in deviation between control participants and PKUlo patients and between control participants and PKUhi patients were $-0.98 (p < .05)$ and $-1.19 (p < .001)$, respectively. Mean differences in standard deviation of the followed trajectory between control participants and PKUlo patients and between control participants and PKUhi patients were $-0.88 (p < .05)$ and $-1.36 (p < .001)$, respectively. No significant differences were observed for the older participants.

The effect of task type differed significantly between control participants and PKU patients, $F(4, 246) = 3.2, p < .05$. PKU patients showed a greater increase in mean deviation from the target in the pursuit task compared with mean deviation from the midline in the tracking task than did control participants, $F(2, 123) = 3.7, p < .05$. The increase of fluctuation in the followed trajectory in the pursuit task compared with the fluctuation in the followed trajectory in the tracking task was greater for PKU patients than for control participants, $F(2, 123) = 2.7, p < .07$ (see Figure 2). A significant interaction was observed between task type and age, $F(2, 122) = 4.5, p < .05$. The significant interaction between task type and group could be attributed to a stronger decrease of accuracy and stability in the pursuit task compared with the tracking task for younger PKU patients compared with age-matched control participants. No differential decreases were observed for the older groups (Figure 2).

A significant part of the observed variance in the analysis of group effects in the tracking and pursuit tasks could be explained by differences in mean RT in the baseline speed task, $F(2, 122) = 36.3, p < .001$. In addition, a significant interaction was observed between within-subjects factor task type and mean RT in the baseline speed task, $F(2, 122) = 33.3, p < .001$, indicating that differences in accuracy and stability between the tracking and pursuit tasks can be partly attributed to different demands with respect to general processing speed. Including mean RT in the baseline speed task as a covariate in the repeated measures procedure did not, however, remove the main effect of group or the significant interaction between task type and group. Adding IQ as a covariate did not remove the main group effect, $F(4, 94) = 3.3, p < .05$, or the interaction between group and task type, $F(4, 94) = 3.9, p < .05$, either. IQ did not explain a significant proportion of the variance of the between- and within-subjects factors.

Associations of Performance With Historical Phe Levels

In Table 2, one-tailed partial correlations are presented of a wide range of possible predictors with the outcome variables of the baseline speed, the tracking and the pursuit tasks for PKU patients. Correlations of mean RT in the baseline speed task with SES and Phe level during the 8th

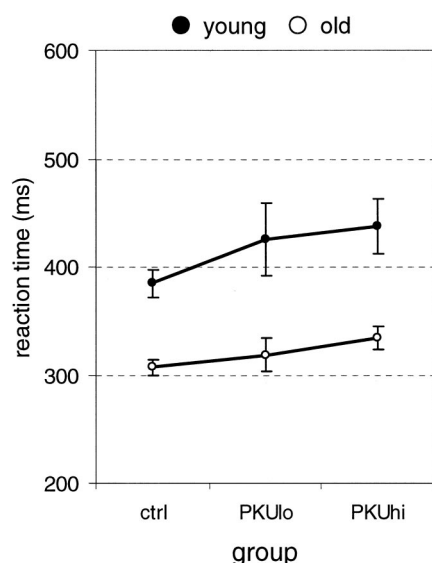


Figure 1. Mean reaction time in the baseline speed task. ctrl = control; PKUlo = low phenylketonuria; PKUhi = high phenylketonuria.

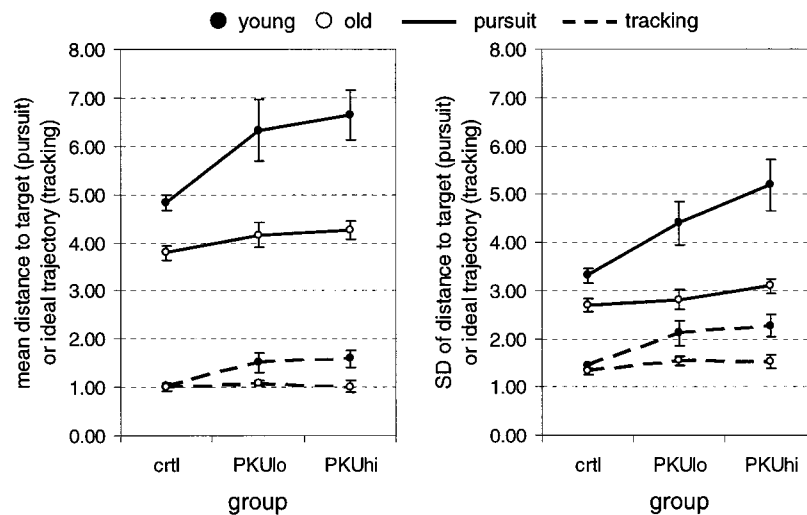


Figure 2. Accuracy (left panel) and stability (right panel) of movement in the tracking and pursuit tasks. ctrl = control; PKUlo = low phenylketonuria; PKUhi = high phenylketonuria.

year of life just reached significance, but no pattern of significant correlations could be detected. Note that the correlation between SES and IDC ($r = -.34$, $p < .05$) was also significant. This may indicate an effect of SES on baseline speed through relatively poor dietary control.

Accuracy in the tracking task was significantly correlated with IQ, SES, IDC, Phe levels at the beginning of life (1st month, 1st year, 2nd year), Phe levels between ages 4 and 6, and Phe level during the 9th year of life. Stability of performance in the tracking task was significantly correlated

with SES, IDC, Phe level in the 1st month of life, and Phe levels between ages 4 and 6. Correlations of performance in the tracking task with Phe levels between ages 4 and 6 were together with IDC the largest. This may indicate the importance of this age period for the development of abilities required by this task. No significant correlation was observed between concurrent Phe level and performance of the tracking task. Concurrent Phe level did not correlate significantly with performance of the pursuit task either. Significant correlations with accuracy and stability in the pursuit

Table 2
Correlations With Performance on Baseline Speed, Tracking, and Pursuit Tasks

Variable	NoP	NoM (SD)	Min	Max	MnVal (SD)	MRT _{bs}	Mndev _{tr}	SD _{tr}	Mndev _{pu}	SD _{pu}
IQ	34				97.3 (11.3)	-0.27	-0.29*	-0.08	-0.27	-0.21
SES	46				1.9 (0.8)	-0.25*	-0.27*	-0.29*	-0.27*	-0.33*
Rphe	61				461.8 (257.5)	0.10	0.06	0.13	0.07	0.14
SOT	56				11.7 (7.8)	-0.01	0.13	0.14	0.12	0.07
IDC	58				345.5 (116.5)	0.14	0.37*	0.26*	0.18	0.18
1 mnth	49				822.8 (492.5)	0.06	0.26*	0.35*	0.11	0.07
yr 1	56	27.4 (9.0)	14	56	311.4 (118.6)	0.05	0.26*	0.19	0.02	-0.08
yr 2	55	12.8 (5.0)	6	29	310.8 (126.8)	0.15	0.25*	0.12	0.05	-0.01
yr 3	57	10.7 (4.5)	3	25	292.4 (129.2)	0.02	-0.03	-0.08	-0.05	-0.07
yr 4	56	10.3 (4.5)	3	21	338.3 (160.5)	0.20	0.21	0.13	0.20	0.10
yr 5	57	9.5 (3.0)	3	20	331.6 (173.9)	0.22	0.37*	0.29*	0.19	0.12
yr 6	58	8.7 (3.0)	2	16	340.9 (173.3)	0.16	0.36*	0.29*	0.22	0.21
yr 7	57	8.5 (3.6)	2	19	370.9 (149.3)	0.20	0.41*	0.31*	0.26*	0.26*
yr 8	53	8.0 (3.3)	2	15	341.3 (137.4)	0.23*	0.18	0.11	0.22	0.30*
yr 9	48	7.8 (2.9)	3	14	354.6 (152.3)	0.07	0.25*	0.04	0.27*	0.36*
yr 10	38	8.0 (3.2)	3	13	354.3 (152.3)	0.00	0.15	0.05	-0.01	0.19

Note. NoP = number of patients on whom mean values and correlations were based; NoM = mean number of phenylalanine (Phe) measurements on which yearly values were based; Min and Max = minimum and maximum number, respectively, of Phe measurements on which yearly values were based; MnVal = mean value; MRT_{bs} = mean reaction time in the baseline speed task; Mndev_{tr} = mean deviation of the midline in the tracking task; SD_{tr} = standard deviation of the followed trajectory in the tracking task; Mndev_{pu} = mean deviation of the ideal trajectory in the pursuit task; SD_{pu} = standard deviation of the followed trajectory in the pursuit task; SES = socioeconomic status (1 = low, 2 = normal, 3 = high); Rphe = phenylalanine level on the day of testing; SOT = start of treatment (days); IDC = Index of Dietary Control (mean of all half-year median Phe levels until the day of testing); 1 mnth = mean Phe level of the 1st month of life; yr 1–yr 10 = mean of half-year medians per year.

* $p \leq .05$.

task were observed for SES and Phe levels between ages 6 and 8 (Table 2). A comparison between the patterns of correlations for the tracking and the pursuit task shows that significant correlations were generally found later in life for the pursuit task. When correlations were calculated for the younger (age < 11 years) and older (age \geq 11 years) PKU patients separately, it became apparent that the correlations were much higher for the younger group.

Discussion

This study confirmed slower information processing in well-treated PKU patients compared with control participants (cf. Burgard et al., 1997). Impaired performance by PKU patients compared with control participants in the tracking and pursuit tasks showed deficiencies in motor control capacity. Although all of the participants showed lower accuracy and stability of movement in the pursuit task compared with the tracking task, performance of the PKU patients deteriorated more than that of the control participants. No influence could be established of Phe level at the time of testing, as was shown by the absence of a significant correlation between concurrent Phe level and measures of performance and the absence of a significant contrast between the PKU patients with Phe levels below 360 $\mu\text{mol/L}$ and those with Phe levels higher than 360 $\mu\text{mol/L}$.

It was hypothesized that PKU patients would show a higher level of impairment in the pursuit task compared with the tracking task, as pursuit requires a higher level of monitoring of movement. As stated earlier, executive function or WM tasks requiring a high level of monitoring and manipulation have shown deficits in treated PKU patients (Diamond et al., 1997; Huijbregts, De Sonnevile, Licht, Van Spronsen, et al., 2002; Huijbregts, De Sonnevile, Licht, Sergeant, & Van Spronsen, 2002; Welsh et al., 1990). The present study shows that deficient performance of PKU patients under higher monitoring demands applies to assessment of motor function. The tracking task was easier to perform than the pursuit task because drawing a circle becomes an increasingly automated action throughout development (see the beginning of the article). Part of the automatization process may be that with practice an increasing number of segments can be organized and executed as a single unit (Van Mier, Hulstijn, & Petersen, 1993). In the pursuit task it is not possible to combine response elements into larger groupings. The trajectory in the pursuit task is unpredictable and the required movements are always new, necessitating more controlled processing (i.e., concurrent planning and execution of movements).

Evidence for DLPFC involvement in novel motor learning (Jueptner et al., 1997; Jueptner & Weiller, 1998; Sakai et al., 1998) and controlled motor processing (Fink et al., 1999; Jeannerod, 1997; Rao et al., 1997; Seitz et al., 2000; Wolpert et al., 1995) supports the hypothesis that motor control in the unpredictable pursuit task requires greater DLPFC involvement than the familiar circular movement in the tracking task. On the basis of the DLPFC's role in cross-temporal mediation (Fuster, 2000), it may be speculated that in the tracking task the discharge of neurons in

response to specific stimulus characteristics (i.e., circle), representing (short-term) active perceptual memory, habituates throughout task performance. In contrast, during the pursuit task the discharge of DLPFC cells reflecting controlled manual responding does not decline during the task.

Preliminary data on DLPFC involvement in the tasks administered in the present study stem from magnetic resonance imaging (MRI) scans of multiple sclerosis (MS) patients, who participated earlier in a neuropsychological study (De Sonnevile et al., 2002). No associations with lesion load were observed for performance of the tracking task. In contrast, performance of the pursuit task was significantly correlated with lesion load at frontal and parietal sites. Application of a strict accuracy criterion in the pursuit task resulted in a significant correlation of only frontal lesion load with accuracy of performance (De Sonnevile & Lazeron, personal communication, April 25, 2002).

The MS data also indicate that DLPFC is not the only brain region differentially involved in the tracking and pursuit tasks. Cortical areas such as the posterior parietal cortex (PPC) may be differentially involved as well. An important role of PPC in the control of limb movement and in eye-hand coordination has often been demonstrated (e.g., Fink et al., 1999; Jeannerod, 1997), as well as a more specific role in continuous tracing tasks comparable with the pursuit task in the present study (Van Mier, Tempel, Perlmutter, Raichle, & Petersen, 1998). Subcortical areas may also be differentially involved in the two tasks. For example, the cerebellum has been shown to be engaged in monitoring and optimizing movements using sensory (proprioceptive) feedback (Fiez, Petersen, Cheney, & Raichle, 1992; Jueptner & Weiller, 1998). There is also evidence for an essential role of the cerebellum in the process by which motor sequences become automatized with practice (Nixon & Passingham, 2000; Thach, 1998).

Similarly, slower speed of processing in PKU patients might be explained by DLPFC dysfunctioning but alternative explanations cannot be ruled out. Swick and Knight (1998) showed disturbed signal-to-noise ratio regulation by DLPFC of visual processing in the extrastriate cortex of participants with DLPFC damage. This function of DLPFC may result in slower speed of responding in simple target detection tasks such as the baseline speed task of the present study. However, myelin deficiencies may explain reduced processing speed as well (Bick et al., 1991; Cleary et al., 1994; Koester, 1991; Rowland, 1991). Reduced vigilance and sustained attention, which have consistently been reported for PKU patients (Burgard et al., 1997; Huijbregts, De Sonnevile, Licht, Van Spronsen, et al., 2002; Schmidt et al., 1996), may also result in slower (mean) processing speed. Reduced levels of noradrenaline (metabolites), which is associated with vigilance and sustained attention (Posner, 1993; Robbins & Everitt, 1994), have been found in the cerebrospinal fluid and autopsied brains of PKU patients (Krause et al., 1985; Lou, Lykkelund, Gerdes, Udesen, & Bruhn, 1987; McKean, 1972). Because vigilance and sustained attention are mediated not only by the locus coeruleus and right parietal areas but by right frontal areas as well (Coull, Frith, Frackowiak, & Grasby, 1996; Pardo,

Fox, & Raichle, 1991), such an explanation of slower processing speed in PKU does not however refute the PFC dysfunction hypothesis.

Although it was found that differences in baseline processing speed explained a significant proportion of the variance of the group effect and the effect of task type in the analysis with the tracking and pursuit tasks, the group effect and the Task \times Group interaction remained significant after mean RT in the baseline speed task was included as a covariate. It has been reported that development of speed of processing explains a considerable part, but not all of the development of WM (Fry & Hale, 1996; Kail & Park, 1994; Miller & Vernon, 1996) and that WM was usually measured by span tasks tapping the maintenance function of WM. Ongoing development of monitoring and manipulation functions may be offered as a possible explanation of variance not explained by development of processing speed.

The results of the present study provide evidence for later development of the abilities required by the pursuit task compared with the tracking task. Accuracy and stability of movements in the tracking and particularly the pursuit task were adversely affected by high Phe levels during rather specific periods of life. Although this result may not mean that different abilities are required by tracking and pursuit (it could also indicate a further refinement of already existing abilities), it underlines the point that pursuit is the more complex task with higher monitoring demands. The finding that the correlations were much higher for PKU patients under the age of 11 than for older patients supports the notion of high Phe levels causing a delay in development, exerting their influence until the start of adolescence.

The finding that current task performance was associated with Phe levels earlier in life in combination with group differences and task-related differences being particularly evident in patients under the age of 11 years supports adherence to a strict low-Phe diet throughout the first 10 years of life after which the diet may be relaxed. These results are in accordance with results from other studies showing the absence (Griffiths, Ward, Harvie, & Cockburn, 1998; Luciana, Sullivan, & Nelson, 2001) or regression (Weglage et al., 1999) of neuropsychological impairments in PKU patients in the age range of 10 to 16, who had been under good dietary control throughout the first decade of life. The PKU patients in the present study had been similarly well controlled as was shown by a mean IDC of 345.5 $\mu\text{mol/L}$. However, ongoing development of manipulation and monitoring functions throughout at least early adolescence should be carefully evaluated in diet relaxation studies. Studies with adult PKU patients who have been well controlled until at least early adolescence should indicate whether diet relaxation is safe and does not lead to cognitive and neurological deficits later in life.

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